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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/965,522	09/26/2001	Preeti Lal	PF-0221-2 DIV	2875

23552 7590 03/19/2004

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/965,522	LAL ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11,12,30-45,56 and 58-60* is/are pending in the application.

4a) Of the above claim(s) *1,12,30,33,35,36,39,44,45 and 56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,31,32,34,37,38,40-43 and 58-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/11/03; 01/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 27, 2004 has been entered.

[2] Claims 1, 11-12, 30-45, 56, and 58-60 are pending in the application.

[3] Applicants' amendment to the claims, filed January 27, 2004, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims in the instant application.

[4] Receipt of an information disclosure statement (IDS), filed January 27, 2004, is acknowledged. The cited references have been considered and a copy of the IDS is attached to the instant Office action.

[5] Claims 1, 12, 30, 33, 35-36, 39, 44-45, and 56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected in invention, there being no allowable generic or linking claim.

[6] Claims 11, 31-32, 34, 37-38, 40-43, and 58-60 are being examined on the merits.

[7] Applicants' arguments, filed January 27, 2004, have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[8] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Rejections - 35 USC § 101

[9] The rejection of claims 11, 31-32, 34, 37-38, 40-43, and 58-60 under 35 U.S.C. 101 is maintained for the reasons of record as set forth in item [10] of the Office action mailed July 29, 2003 and for the reasons stated below. The examiner maintains the position that the claimed invention is not supported by either a specific and substantial asserted utility or well-established utility.

Applicants argue the examiner has not established a prima facie case of lack of utility and assert that one would find the asserted utility more likely than not to be true and that absolute certainty is not required. Applicants' arguments are not found persuasive and are addressed in detail below.

Specifically, applicants argue that the study of Brenner et al. (*PNAS* 95:6073-6078; cited by applicants in the IDS filed April 11, 2003) validated the use of sequence comparison methods to establish that % sequence identity comparisons >30% are predictive of shared function and that the teachings of Brenner et al. validates the establishment of the utility of NAPTR based on 48% amino acid sequence identity to NPT1. Applicants' argument is not found persuasive.

The teachings of Brenner et al. nowhere address assigning function of NAPTR based on identity to NPT1. In this regard, applicants are invited to direct the examiner's attention to such teachings. In the absence of such teachings, the reference of Brenner et al. is inapposite to the instant rejection and does not support applicants' argument. The utility requirement requires a claimed invention to be available in a currently available form. However, in this case, there is no way of knowing the biological activity and/or significance of the polypeptide of SEQ ID NO:1 based on the disclosure. Applicants do not dispute that NAPTR may have a function other than that of NPT1 – there is clearly no way of knowing the biological activity and/or significance based on sequence comparison alone. Even assuming arguendo that Brenner et al. (*PNAS)* was relevant to the instant rejection – which it is not – one of skill in the art would recognize that the teachings of Brenner et al. (*PNAS*) do not address the likely possibility that the polypeptide of SEQ ID NO:1 has no biological function, i.e., it is biologically inactive. One of skill in the art recognizes that empirical evidence is required to first ascertain the presence of a biological activity and to further ascertain which biological activity is exhibited by a given polypeptide as clearly supported by Brenner (*Trends Genet*) and Scott et al. (cited in the Office action mailed July 29, 2003). Sequence comparison alone provides zero indication of the presence of biological activity and, in the instant case, provides only a weak prediction as to which biological activity is exhibited by SEQ ID NO:1.

Applicants argue that the examiner is requiring applicants to establish utility to a higher degree of certainty than is required. Applicants argue that all that is necessary is that one would conclude that the asserted utility is more likely than not true and that the provided evidence establishes that the asserted

utility is more likely than not to be true. Applicants identify such evidence as chemical and structural homology between NAPTR and NPT1 and the known function of NPT1. Applicants argue that Ishibashi et al. (cited by applicants in the IDS filed January 27, 2004) disclose a polypeptide that shares 44% amino acid sequence identity to NPT1 and about 70% identity to SEQ ID NO:1 and has the ability to mediate phosphate transport across a cell membrane. Applicants argue that sequence identity is a reliable technique for identifying Type I phosphate cotransporters and would conclude that the specification has established that it is more likely than not true that the polypeptide of SEQ ID NO:1 shares the same phosphate transport function as NPT1 or belongs to the Type 1 class of phosphate transporters. Applicants' argument is not found persuasive.

As stated above, there is no evidence of record that would indicate that the polypeptide of SEQ ID NO:1 has any biological activity – applicants are invited to provide evidence of such. Furthermore, applicants do not dispute the teachings of Brenner (*Trends Genet*) and Scott et al., who provide evidence that sequence analysis alone is not enough to ascertain the function of a polypeptide. Because applicants have failed to demonstrate the presence of biological activity, it follows that applicants have also failed to show that SEQ ID NO:1 has phosphate cotransporter activity. Regarding the reference of Ishibashi et al., it is noted that this reference was not available at the time of filing of the instant application and a skilled artisan would not have been able to consider such evidence. Nonetheless, there are several points that should be made of record regarding the reference of Ishibashi et al. that are relevant to the instant rejection. These are as follows: 1) Based on sequence homology, Ishibashi et al. assign their polypeptide as a homolog of human NPT4 (page 11, left column, middle), not NPT1 and, interestingly, the polypeptide of SEQ ID NO:1 shares a higher degree of sequence identity to rNPT4 than to NPT1 (SEQ ID NO:1 shares 48% identity with NPT1 and 70% to rNPT4); 2) there is significant variability even among members of Type I phosphate co-transporters (page 18, top); 3) Ishibashi et al. acknowledge that the physiological importance of NPT1 is not clear (page 10, right column); 4) Ishibashi et al. recognized that mere sequence analysis alone is not enough to assign function to rNPT4 and instead confirm function using an assay "[t]o determine whether rNPT4 functions as Na/Pi co-transporter" (page 13, Figure 2 and left column, middle); and 5) Ishibashi et al. address the possibility of non-functional splice variants of

human phosphate cotransporter (page 13, left column, top), thus providing evidence that SEQ ID NO:1 may be non-functional.

Applicants argue that antibodies to a polypeptide of SEQ ID NO:1 are useful in the purification of SEQ ID NO:1 and/or diagnosis of disorders associated with increased/decreased expression of NAPTR as disclosed at page 22, lines 16-25 of the specification. Applicants' argument is not found persuasive.

Regarding the use of an antibody to SEQ ID NO:1 as a purification reagent, it is noted that this use is not specific as any antibody can be used in the purification of its cognate polypeptide. Regarding the use of an antibody to SEQ ID NO:1 for diagnosis, it is noted that there is no evidence of record that would indicate that altered NAPTR expression is correlated with any disease state, particularly those that are disclosed in the specification – applicants are invited to provide evidence of such in the specification – and the specification fails to provide the necessary guidance that would enable a skilled artisan to use the claimed antibody for such diagnosis. Further experimentation is required to identify which – if any – disease state can be diagnosed using the claimed invention.

Applicants argue that the specification discloses administering an antibody that antagonizes or inhibits phosphate uptake, such as an antibody to NAPTR, could be exploited to treat increased phosphate levels in brain or kidney. Applicants' argument is not found persuasive.

There is no evidence of record that NAPTR is involved in abnormal phosphate regulation – applicants are invited to provide evidence of such in the specification – and the specification fails to provide the necessary guidance that would enable a skilled artisan to use the claimed antibody for successfully treating a disease using the claimed antibody, e.g., dosage, route of administration, toxicity, and regions specific to SEQ ID NO:1 that do not significantly cross-react with other proteins.

Claim Rejections - 35 USC § 112, First Paragraph

[10] The enablement rejection of claims 11, 31-32, 34, 37-38, 40-43, and 58-60 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth in item [11] of the Office action mailed July 29, 2003 and for the reasons stated below. The examiner maintains the position that, since the

claimed invention is not supported by either a substantial or specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants assert a specific utility for SEQ ID NO:1 based on chemical and structural homology between NAPTR and NPT1 and the known function of NPT1. Applicants argue that Ishibashi et al. (cited by applicants in the IDS filed January 27, 2004) disclose a polypeptide that shares 44% amino acid sequence identity to NPT1 and about 70% identity to SEQ ID NO:1 and has the ability to mediate phosphate transport across a cell membrane. Applicants argue that sequence identity is a reliable technique for identifying Type I phosphate cotransporters and would conclude that the specification has established that it is more likely than not true that the polypeptide of SEQ ID NO:1 shares the same phosphate transport function as NPT1 or belongs to the Type 1 class of phosphate transporters. Applicants' argument is not found persuasive.

Applicants' assertion that SEQ ID NO:1 has a specific utility (page 11, lines 23-24 of the amendment filed January 27, 2004 is acknowledged. However, it should be noted that the issue at hand is the utility of the claimed antibody, not the utility of SEQ ID NO:1. There is no evidence of record that would indicate that the polypeptide of SEQ ID NO:1 has any biological activity – applicants are invited to provide evidence of such. Furthermore, applicants do not dispute the teachings of Brenner (*Trends Genet*) and Scott et al., who provide evidence that sequence analysis alone is not enough to ascertain the function of a polypeptide. Because applicants have failed to demonstrate the presence of biological activity, it follows that applicants have also failed to show that SEQ ID NO:1 has phosphate cotransporter activity. Regarding the reference of Ishibashi et al., it is noted that this reference was not available at the time of filing of the instant application and a skilled artisan would not have been able to consider such evidence. Nonetheless, there are several points that should be made of record regarding the reference of Ishibashi et al. that are relevant to the instant rejection. These are as follows: 1) Based on sequence homology, Ishibashi et al. assign their polypeptide as a homolog of human NPT4 (page 11, left column, middle), not NPT1 and, interestingly, the polypeptide of SEQ ID NO:1 shares a higher degree of sequence identity to rNPT4 than to NPT1 (SEQ ID NO:1 shares 48% identity with NPT1 and 70% to

rNPT4); 2) there is significant variability even among members of Type I phosphate co-transporters (page 18, top); 3) Ishibashi et al. acknowledge that the physiological importance of NPT1 is not clear (page 10, right column); 4) Ishibashi et al. recognized that mere sequence analysis alone is not enough to assign function to rNPT4 and instead confirm function using an assay "[t]o determine whether rNPT4 functions as Na/Pi co-transporter" (page 13, Figure 2 and left column, middle); and 5) Ishibashi et al. address the possibility of non-functional splice variants of human phosphate cotransporter (page 13, left column, top), thus providing evidence that SEQ ID NO:1 may be non-functional.

Applicants argue that antibodies to a polypeptide of SEQ ID NO:1 are useful in the purification of SEQ ID NO:1 and/or diagnosis of disorders associated with increased/decreased expression of NAPTR as disclosed at page 22, lines 16-25 of the specification. Applicants' argument is not found persuasive.

Regarding the use of an antibody to SEQ ID NO:1 as a purification reagent, it is noted that this use is not specific as any antibody can be used in the purification of its cognate polypeptide. Regarding the use of an antibody to SEQ ID NO:1 for diagnosis, it is noted that there is no evidence of record that would indicate that altered NAPTR expression is correlated with any disease state, particularly those that are disclosed in the specification – applicants are invited to provide evidence of such in the specification – and the specification fails to provide the necessary guidance that would enable a skilled artisan to use the claimed antibody for such diagnosis. Further experimentation is required to identify which – if any – disease state can be diagnosed using the claimed invention.

Applicants argue that the specification discloses administering an antibody that antagonizes or inhibits phosphate uptake, such as an antibody to NAPTR, could be exploited to treat increased phosphate levels in brain or kidney. Applicants' argument is not found persuasive.

There is no evidence of record that NAPTR is involved in abnormal phosphate regulation – applicants are invited to provide evidence of such in the specification – and the specification fails to provide the necessary guidance that would enable a skilled artisan to use the claimed antibody for successfully treating a disease using the claimed antibody, e.g., dosage, route of administration, toxicity, and regions specific to SEQ ID NO:1 that do not significantly cross-react with other proteins.

[11] In view of applicants' amendment to the claims, the written description rejection of claims 11, 31, 32, 34, 42-43, and 58 under 35 U.S.C. 112, first paragraph, as set forth in item [12] of the Office action mailed July 29, 2003, is withdrawn.

[12] Even if applicants demonstrate an antibody to SEQ ID NO:1 has a specific and substantial or well-established utility, the following rejection still applies. Claim(s) 11, 31-32, 34, 37-38, 40-43, and 58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody that binds to SEQ ID NO:1, does not reasonably provide enablement for all antibodies that bind to a polypeptide comprising or having SEQ ID NO:1 as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: The claims are so broad as to encompass all antibodies that bind to a polypeptide comprising or having SEQ ID NO:1 as broadly encompassed by the claims. The broad scope of claimed antibodies is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of antibodies broadly encompassed by the claims. As the terms "comprising" and "having" are open claim language, the claims are not limited to an antibody that binds SEQ ID NO:1 and instead encompass all antibodies that bind polypeptides comprising or having

the amino acid sequence of SEQ ID NO:1. In this case the enablement provided by the disclosure is limited to an antibody that binds to SEQ ID NO:1.

- The lack of guidance and working examples: The specification provides only a single working example of the claimed antibody, *i.e.*, an antibody that binds SEQ ID NO:1. This single working example fails to provide the necessary guidance for making and/or using the broad scope of claimed antibodies. The specification provides no guidance or assurance of success in adding amino acids at the N- and/or C-terminus of SEQ ID NO:1 with an expectation that the resulting cognate antibody will maintain the ability to bind SEQ ID NO:1.

- The high level of unpredictability in the art: The ability of an antibody to bind a particular epitope within a polypeptide is dependent upon the amino acid sequence of the polypeptide and, if the polypeptide is in its native state, *i.e.,* non-denatured, the resulting conformation acquired by the amino acid sequence (see Abaza et al. *J Protein Chem* 11:433-444 who teach that "the reaction of a protein antigen with its antibodies is influenced by conformational changes" (page 436, left column, bottom to right column, top)). It is highly unpredictable as to the effects of amino acid addition at the N- and/or C-terminus of a polypeptide on the binding of a cognate antibody.

- The state of the prior art supports the high degree of unpredictability: The state of the art provides evidence for the high degree of unpredictability that an antibody, *e.g.,* an antibody that binds SEQ ID NO:1, will bind to an altered polypeptide sequence, *e.g.,* SEQ ID NO:1 with additional amino acids at the N- and/or C-terminus. For example, Abaza et al. (*J Protein Chem* 11:433-444) teach that alterations outside of the boundaries of an antigenic site can significantly affect antibody binding (page 443, right column to page 444, left column) and one of skill in the art recognizes that additional amino acids at the N- and/or C-terminus of a polypeptide can affect its conformation, which in turn can affect antibody binding as evidenced by Abaza et al. (page 436, left column, bottom to right column, top).

- The amount of experimentation required is undue: While methods of generating antibodies against an antigen are known, it is not routine in the art to screen for all antibodies that bind amino acid

sequences having any number of N- and/or C-terminal additions as encompassed by the instant claims. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicant argues that the rejection is overcome by amendment. However, the examiner maintains the position that undue experimentation is required to make the broad scope of claimed antibodies for the reasons stated above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[13] Claims 11, 31-32, 34, 42-43, and 59-60 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Feder et al. (US Patent 5,872,237). The claims are drawn to an isolated antibody that binds to a polypeptide comprising or consisting of SEQ ID NO:1.

Feder et al. teach a polypeptide, NPT4 (see Appendix A), that is 99.3% identical to the polypeptide of SEQ ID NO:1 having two mismatches and one conservative substitution (see Appendix A).

Feder et al. teach methods of generating antibodies using their polypeptide and use thereof for immunoassay (see columns 15-16). Feder et al. do not specifically teach an isolated antibody that binds NPT4.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to generate and isolate an antibody to NPT4. One would have been motivated to produce and isolate an antibody to NPT4 in order to use the antibody in an immunoassay as taught by Feder et al. One would have a reasonable expectation of success for producing and isolating an antibody to NPT4 because of the results of Feder et al. Therefore, claims 11, 31-32, 34, 42-43, and 59-60, drawn to an antibody as described above would have been obvious to one of ordinary skill in the art.

While it is acknowledged that NPT4 is not 100% identical to SEQ ID NO:1, one of ordinary skill in the art would recognize that an antibody that binds NPT4 would also bind to SEQ ID NO:1. Since the Office does not have the facilities for examining and comparing applicants' antibody with the antibody made obvious by the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the antibody made obvious by the prior art does not possess the same material structural and functional characteristics of the claimed antibody). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

Conclusion

[14] Status of the claims:

- Claims 1, 11-12, 30-45, 56, and 58-60 are pending.
- Claims 1, 12, 30, 33, 35-36, 39, 44-45, and 56 are withdrawn from consideration.
- Claims 11, 31-32, 34, 37-38, 40-43, and 58-60 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-

0928. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652
03-16-04

APPENDIX A

```
RESULT 3
US-08-724-394A-11
; Sequence 11, Application US/08724394A
; Patent No. 5872237
;  GENERAL INFORMATION:
;    APPLICANT:  Feder, John N.
;    APPLICANT:  Kronmal, Gregory S.
;    APPLICANT:  Lauer, Peter M.
;    APPLICANT:  Ruddy, David A.
;    APPLICANT:  Thomas, Winston
;    APPLICANT:  Tsuchihashi, Zenta
;    APPLICANT:  Wolff, Roger K.
;    TITLE OF INVENTION:  Megabase Transcript Map:  No. 5872237el
;    TITLE OF INVENTION:  Sequences and Antibodies Thereto
;    NUMBER OF SEQUENCES:  31
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  TOWNSEND and TOWNSEND and CREW LLP
;      STREET:  Two Embarcadero Center, 8th Floor
;      CITY:  San Francisco
;      STATE:  CA
;      COUNTRY:  USA
;      ZIP:  94111-3834
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  PatentIn Release #1.0, Version #1.30
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/724,394A
;      FILING DATE:  01-OCT-1996
;      CLASSIFICATION:  536
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  Fitts, Renee A.
;      REGISTRATION NUMBER:  35,136
;      REFERENCE/DOCKET NUMBER:  017957-000100
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  415-576-0200
;      TELEFAX:  415-576-0300
;  INFORMATION FOR SEQ ID NO:  11:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  480 amino acids
;      TYPE:  amino acid
;      STRANDEDNESS:  not relevant
;      TOPOLOGY:  not relevant
;    MOLECULE TYPE:  peptide
;    FEATURE:
;      NAME/KEY:  Region
;      LOCATION:  1..480
;      OTHER INFORMATION:  /note= "NPT4"
US-08-724-394A-11

  Query Match             95.9%;  Score 1991.5;  DB 2;  Length 480;
  Best Local Similarity   82.9%;  Pred. No. 3.3e-201;
  Matches  398;  Conservative    1;  Mismatches    2;  Indels   79;  Gaps    3;

Qy          1 MQVDETLIPRKVPSLCSARYGIALVLHFCNFTTIAQNVIMNITMVAMVNSTSPQSQLNDS 60
              ||||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MQVDETLIPRKGPSLCSARYGIALVLHFCNFTTIAQNVIMNITMVAMVNSTSPQSQLNDS 60

Qy         61 SE-------------------------------------------VLPVDSFGGLSKA 75
              ||                                           ||||||||||||
Db         61 SEXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXVLPVDSFGGLSKA 120

Qy         76 PKSLP---------------------------------AKSSILGGQFAIWERWGPPQER 102
              |||||                               |||||||||||||:|||||||
Db        121 PKSLPXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXAKSSILGGQFAIWEKWGPPQER 180
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Qy        103 SRLCSIALSGMLLGCFTAILIGGFISETLGWPFVFYIFGGVGCVCCLLWFVVIYDDPVSY 162
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||| ||
Db        181 SRLCSIALSGMLLGCFTAILIGGFISETLGWPFVFYIFGGVGCVCCLLWFVVIYDDPFSY 240

Qy        163 PWISTSEKEYIISSLKQQVGSSKQPLPIKAMLRSLPIWSICLGCFSHQWLVSTMVVYIPT 222
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 PWISTSEKEYIISSLKQQVGSSKQPLPIKAMLRSLPIWSICLGCFSHQWLVSTMVVYIPT 300

Qy        223 YISSVYHVNIRDNGLLSALPFIVAWVIGMVGGYLADFLLTK-KFRLITVRKIATILGSLP 281
              |||||||||||||||||||||||||||||||||||||||| ||||||||||||||||||
Db        301 YISSVYHVNIRDNGLLSALPFIVAWVIGMVGGYLADFLLTKXKFRLITVRKIATILGSLP 360

Qy        282 SSALIVSLPYLNSGYITATALLTLSCGLSTLCQSGIYINVLDIAPRYSSFLMGASRGFSS 341
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 SSALIVSLPYLNSGYITATALLTLSCGLSTLCQSGIYINVLDIAPRYSSFLMGASRGFSS 420

Qy        342 IAPVIVPTVSGFLLSQDPEFGWRNVFFLLFAVNLLGLLFYLIFGEADVQEWAKERKLTRL 401
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 IAPVIVPTVSGFLLSQDPEFGWRNVFFLLFAVNLLGLLFYLIFGEADVQEWAKERKLTRL 480
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NPT1    MQMDNRLPPKKVPGFCSFRYGLSFLVHCCNVIITAQRACLNLTMVVMVNSTDPHGLPNTSTKKLLDNIKN----------
NPT3    ---MDGKPATRKGPDFCSLRYGLALIMHFSNFTMITQRVSLSIAIIAMVNITQQQGLSNASTEGPVADAFNNSSISIKEFDTK
NPT4    MQVDETLIPRKGPSLCSARYGIALVLHFCNFTTIAQNVIMNITMVAMVNSTSPQSQLNDSSE----------
                *     * * ** ***    * *   *          *** *      * *

NPT1    -PMYNWSPDIQFIILSSTSYGVIIIQVPVGYFSGIYSTKKMIGFALCLSSVLSLLIPPAAGIGVAWVVVCRAVQGAAQGIVA
NPT3    ASVYQWSPETQGIIFSSINYGIILTLIPSGYLAGIFGAKKMLGAGLLISSLLTLFTPLAADFGVILVIMVRTVQGMAQGMAW
NPT4    ----------VLPVDSFGGLSKAPKSLP----------AKSSIL
                            *    *    *

NPT1    TAQFEIYVKWAPPLERGRLISMSTSGFLLGPFIVLLVTGVICESLGWPMVFYIFGACGCAVCLLWFVLFYDDPKDHPCISIS
NPT3    TGQFTIWAKWAPPLERSKLTIIAGSCSAFGSFIILCVGGLISQALSWPFIFYIFGSTGCVCCLLWFTVIYDDPMHHPCISVR
NPT4    GGQFAIWEKWGPPQERSRLCSIALSGMLLGCFTAILIGGFISETLGWPFVFYIFGGVGCVCCLLWFVVIYDDPFSYPWISTS
          ** *  ** ** **  *     **  * *     *   * ** *****  **  *****  **** * **

NPT1    EKEYITSSLVQQVSSSRQSLPIKAILKSLPVWAISIGSFTFFWSHNIMTLYTPMFINSMLHVNIKENGFLSSLPYLFAWICG
NPT3    EKEHILSSLAQQPSSPGRAVPIKAMVTCLPLWAIFLGFFSHFWLCTIILTYLPTYISTLLHVNIRDSGVLSSLPFIAAASCT
NPT4    EKEYIISSLKQQVGSSKQPLPIKAMLRSLPIWSICLGCFSHQWLVSTMVVYIPTYISSVYHVNIRDNGLLSALPFIVAWVIG
        *** * *** **  *     ****   ** * *  * *     *       * *  *   ****   * ** **   *

NPT1    NLAGQLSDFFLTRNILSVIAVRKLFTAAGFLLPAIFGVCLPYLSSTFYSIVIFLILAGATGSFCLGGVFINGLDIAPRYFGF
NPT3    ILGGQLADFLLSRNLLRLITVRKLFSSLDMQVSSWE----------SQGDLGSSQES SLPLPLDSSS-----
NPT4    MVGGYLADFLLTK-KFRLITVRKIATILGSLPSSALIVSLPYLNSGYITATALLTLSCGLSTLCQSGIYINVLDIAPRYSSF
          * * ** *      * ***                                                **

NPT1    IKACSTLTGMIGGLIASTLTGLILKQDPESAWFKTFILMAAINVIGLIFYLIVATAEIQDWAKEKQHTRL
NPT3    ----VRILSLVGGMSFSCLL-----QSTCLAWSFTSRLDKQNFKTGPKRGPLPASEDIKLQT --------
NPT4    LMGASRGFSSIAPVIVPTVSGFLLSQDPEFGWRNVFFLLFAVNLLGLLFYLIFGEADVQEWAKERKLTRL
                              *    *    *    *
```